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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/707,730	11/06/2000	Craig Hill	16778-704	8812

24353 7590 10/21/2003

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EXAMINER	
LANDSMAN, ROBERT S	
ART UNIT	**PAPER NUMBER**
1647	19

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/707,730	Applicant(s) HILL ET AL.	
	Examin r Robert Landsman	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *35,36,39,40,43 and 44* is/are allowed.

6)☒ Claim(s) *25-34,37,38,41 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: Art of Interest

DETAILED ACTION

1. Formal Matters

A. Amendment B, filed 8/7/03, has been entered into the record.

B. Claims 25-40 are pending in the application. Claims 41-44 have been added in Amendment B. Therefore, claims 25-44 are pending and are the subject of this Office Action.

C. All Statutes under 35 USC not found in this Office Action can be found, cited in full, in a previous Office Action.

2. Information Disclosure Statement

A. Applicants request that the Examiner initial and return the PTO SB-08A submitted with the IDS of May 20, 2003 as well as the electronic IDS filed August 7, 2003. The IDS filed 5/20/03 has been initialed and returned with this Office Action. However, neither the SB-08 nor the electronic IDS could be found. However, after the mailing of this Office Action, this entire application will be scanned and available electronically. Therefore, the two missing forms may appear at this time.

3. Specification

A. Applicants have amended the first line of the specification to recite that the present application is a 09/217,037.

3. Claim Rejections - 35 USC § 112, first paragraph –scope of enablement

A. The rejection of claims 25-40 under 35 USC 112, first paragraph, has been withdrawn in view of the fact that Applicants' invention is limited to specific steroid-neurotrophin conjugates and that the artisan knows how to administer these compounds.

B. Claims 25-34, 37 and 38 are rejected and new claims 41 and 42 are also rejected under 35 USC 112, first paragraph, because the specification, while being enabling for the claimed steroids conjugated to NGF, or a receptor binding fragment thereof, does not reasonably provide enablement for any binding fragment of any neurotrophin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

First, the breadth of the claims is excessive with regard to Applicants claiming any steroid conjugate comprising neurotrophin receptor binding fragment thereof, other than NGF. Applicants have only provided guidance and working examples of receptor binding fragments of NGF (page 18 of the specification). However, Applicant provide no guidance or working examples of any other neurotrophin receptor binding fragment. In the absence of this guidance, it would not be predictable to the artisan which residues of these other neurotrophins would need to be maintained in order to maintain their receptor binding characteristics. Applicants have only taught on lines 20-22 of page 18 that certain BNDF, NT3, 4 and 5 analogs can bind neurotrophin receptors. However, these analogs appear to be distinct from the actual protein fragments.

Therefore, given the excessive breadth of the claims along with the lack of guidance and working examples of any neurotrophin receptor binding fragment other than NGF as well as the unpredictability as to which amino acid residues are required to bind to the neurotrophin receptor, the Examiner holds that undue experimentation is required to practice the invention as claimed.

4. Claim Rejections - 35 USC § 112, second paragraph

A. The rejection of claims 34-40 under 35 USC 112, second paragraph, has been withdrawn in view of Applicants' amendment to these claims to spell out the names of the neurotrophins.

5. Art of Interest

A. The Examiner apologizes that the Art of Interest was not included in the previous Office Action. A copy has been provided herewith. Not all of the art of interest is pertinent in this situation since many of the references have been published after the filing date of the parent. The Examiner will place pertinent references on a Form-892 in the next Office Action. However, the Examiner would like an explanation as to what the invention discloses over the prior art. As stands, it appears obvious to the artisan to produce conjugates of steroids and neurotrophins since these steroids affect at least neurotrophin expression (see for example #16 of 26 on the Art of Interest). Therefore, it appears obvious for the artisan to administer this conjugate in a patient who requires increased neurotrophins. The highlighted references demonstrates how to identify the reference number and reference.

6. Conclusion

A. It appears that claims 35, 39, 39, 40, 43 and 44 are allowable, but the Examiner agrees that a telephone interview may help clarify any potential issues regarding obviousness of these claims as well as to expedite the identification of other allowable subject matter. Applicants may telephone the Examiner at their earliest convenience.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
October 20, 2003

ROBERT LANDSMAN
PATENT EXAMINER

Art of Interest

=> dup rem l10

PROCESSING COMPLETED FOR L10
L11 26 DUP REM L10 (21 DUPLICATES REMOVED)

=> d ti abs so l11 1-26

L11 ANSWER 2 OF 26 CAPLUS COPYRIGHT 2003 ACS
TI Use of non-immunosuppressive compounds which disrupt the steroid receptor complex for promoting nerve regeneration, screening method, pharmaceutical compositions, and therapeutic use
AB This invention takes advantage of the finding that neurite outgrowth and nerve regeneration are promoted by disruption of the steroid receptor complex. This disruption can take the form of disruption of the phys. assembly or function of the steroid receptor complex, such as the mature complex or a precursor of the mature complex that is required for assembly of the mature complex. Geldanamycin and its analogs, as well as FKBP-52 antibody, are shown to disrupt the complex and promote nerve growth. In addn. to these compds., the invention includes assays for finding neurotrophic compds., as well as compds. found by these assays, pharmaceutical compns. into which they are incorporated, and methods of treating subjects having neuronal dysfunction caused by injury or disease.
SO PCT Int. Appl., 55 pp.
CODEN: PIXXD2

L11 ANSWER 3 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Effects of **dexamethasone** (DEX) on growth factor and **neurotrophin** mRNA expression by cultured human trabecular meshwork cells.
SO IOVS, (**March 15, 1999**) Vol. 40, No. 4, pp. S667.
Meeting Info.: Annual Meeting of the Association for Research in Vision and Ophthalmology Fort Lauderdale, Florida, USA May 9-14, 1999 Association for Research in Vision and Opthalmology

L11 ANSWER 4 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
TI Glucocorticoid regulation of motoneuronal parameters in rats with spinal cord injury.
AB 1. Glucocorticoids exert beneficial effects after acute CNS injury in humans and experimental animals. To elucidate potential mechanisms of glucocorticoid action in the lesioned spinal cord, we have studied if treatment with **dexamethasone** (DEX) modulated the **neurotrophin** binding receptor p75 (p75NTR) and choline acetyltransferase (ChAT), a marker of neuronal functional viability. 2. Rats with a sham operation or with spinal cord transection at the thoracic level received vehicle or DEX several times postlesion and were sacrificed 48 hr after surgery. The lumbar region caudal to the lesion was processed for p75NTR and ChAT immunoreactivity (IR) using quantitative densitometric analysis. 3. We observed that p75NTR-IR was absent from ventral horn motoneurons of sham-operated rats, in contrast to strong staining of neuronal perikaryon in TRX rats. Administration of DEX to TRX rats had no

effect on the number of neuronal cell bodies expressing p75NTR-IR but significantly increased the number and length of immunostained neuronal processes. 4. Furthermore, spinal cord transection reduced ChAT immunostaining of motoneurons by 50%, whereas DEX treatment reverted this pattern to cells with a strong immunoreaction intensity in perikaryon and cell processes. 5. It is hypothesized that increased expression of p75NTR in cell processes and of ChAT in motoneurons may be part of a mechanism by which glucocorticoids afford neuroprotection, in addition to their known antiinflammatory effects.

SO Cellular and Molecular Neurobiology, (**Oct., 1999**) Vol. 19, No. 5, pp. 597-611.
ISSN: 0272-4340.

L11 ANSWER 5 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2

TI A possible mechanism of TPA-mediated downregulation of **neurotrophin**-3 gene expression in rat cultured vascular smooth muscle cells.

AB We have previously reported that in cultured rat vascular smooth muscle cells (VSMCs), **neurotrophin**-3 (NT-3) gene expression was suppressed by TPA (12-O-tetradecanoyl phorbol-13-acetate), which induces an AP-1 transcription factor. In the present study, to clarify the mechanism for TPA-mediated downregulation of NT-3 gene expression, effects of cycloheximide and **dexamethasone** (Dex) on the TPA-mediated downregulation were examined in VSMCs. Pretreatment with cycloheximide, an inhibitor of protein synthesis, or simultaneous treatment with Dex, an inhibitor of AP-1, suppressed the TPA-mediated downregulation of NT-3 gene expression. Furthermore, co-transfection of c-fos and c-jun expression vectors into VSMCs resulted in decrease in the NT-3 gene expression. The present findings suggest that TPA-induced AP-1 de novo synthesis causes the downregulation of NT-3 gene expression in VSMCs.

SO Molecular Brain Research, (**May 7, 1999**) Vol. 68, No. 1-2, pp. 186-189.
ISSN: 0169-328X.

L11 ANSWER 6 OF 26 MEDLINE

TI Regulation of NGFI-A (Egr-1) gene expression by the POU domain transcription factor Brn-3a.

AB NGFI-A is an immediate early gene (IEG) that is transcriptionally induced by nerve growth factor (NGF) in PC12 cells and has been implicated in a number of cellular responses. Studies have shown that elements within the first 106 base pairs of the NGFI-A promoter contribute to its induction by NGF in PC12 cells. One element, within the serum response element (SRE) bridge region, bears strong homology to a motif previously identified in promoters regulated by the Brn-3a POU domain transcription factor. We report here that Brn-3a activates the NGFI-A promoter in neurons (both primary and cell lines). Analysis revealed that this response requires sequences between positions -49 and -106. Whilst DNA-protein interaction studies failed to identify a site bound directly by Brn-3a, the data presented here suggest that Brn-3a may cooperate in the regulation of NGFI-A gene expression in neurons, possibly during the developmental switch between **neurotrophin** dependency that occurs during neurogenesis.

SO BRAIN RESEARCH. MOLECULAR BRAIN RESEARCH, (**1999 Dec 10**) 74 (1-2) 117-25.
Journal code: 8908640. ISSN: 0169-328X.

L11 ANSWER 7 OF 26 CAPLUS COPYRIGHT 2003 ACS
TI Mononuclear phagocytes and their use to promote axonal regeneration
AB Methods and compns. are disclosed for the use of allogeneic mononuclear phagocytes to promote axonal regeneration in the central nervous system of a mammal. In one embodiment, allogeneic mononuclear phagocytes are administered into the CNS at or near a site of injury or disease and the mammal is treated with at least one anti-inflammatory agent. In another embodiment, allogeneic mononuclear phagocytes are administered into the CNS at or near a site of injury or disease and one or more enumerated adjuvant factors (e.g. aFGF) are administered to the CNS; anti-inflammatory therapy of the mammal may optionally be added. In a further embodiment, allogeneic mononuclear phagocytes are first stimulated with one or more enumerated stimulatory factors and then administered into the CNS at or near a site of injury or disease. Methods for screening stimulatory tissue and cells are also disclosed. Use of monocytes to promote axonal regeneration in transected optic nerve is described.
SO PCT Int. Appl., 70 pp.
CODEN: PIXXD2

L11 ANSWER 8 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3
TI **Dexamethasone** induces hypertrophy of developing medial septum cholinergic neurons: Potential role of nerve growth factor.
AB Glucocorticoid hormones influence neuronal plasticity during development; however little is known about the mechanisms of this trophic activity. Because glucocorticoids increase nerve growth factor (NGF) synthesis in selected brain areas and NGF plays a role in the development of basal forebrain cholinergic neurons, we tested the hypothesis that glucocorticoids may foster maturation of the cholinergic phenotype during postnatal development via the induction of NGF biosynthesis. The synthetic glucocorticoid **dexamethasone** (DEX) was injected systemically (0.5 mg/kg, s.c.) once a day for 1 week in 7-d-old (P7) rats. DEX elicited an increase in NGF mRNA and protein levels in the cerebral cortex and hippocampus as well as specific NGF responses, such as TrkA tyrosine phosphorylation in the septum, choline acetyltransferase (ChAT) and p75 **neurotrophin** receptor (p75NTR) immunoreactivity, and a relative number of cholinergic neurons in the medial septum. To examine whether the effect of DEX is age-related, we treated 1- and 14-d-old rats with DEX for 1 week. DEX increased NGF expression in rats treated from P1 to P8 but not in those treated from P14 to P21. The age-related increased expression of NGF correlated with the induction of ChAT immunoreactivity in the medial septum. Moreover, in the spinal cord, neither NGF nor ChAT levels were increased by DEX, suggesting that the glucocorticoid-mediated changes seen in the basal forebrain are associated with specific NGF responses. Our data suggest that by increasing NGF levels, glucocorticoids may play a role in the maturation of postnatal cholinergic neurons.
SO Journal of Neuroscience, (**Nov. 15, 1998**) Vol. 18, No. 22, pp. 9326-9334.
ISSN: 0270-6474.

L11 ANSWER 9 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE

4
TI **Dexamethasone** inhibits ischemia-induced transient reduction of **neurotrophin**-3 mRNA in rat hippocampal neurons.
AB **Dexamethasone** (DEX) increases the expression of **neurotrophin**-3 (NT-3) in normal rat hippocampal neurons, whereas transient forebrain ischemia reduces the NT-3 mRNA level. The effect of DEX on the expression of NT-3 mRNA in injured brain cells after ischemia has not been investigated, however. Using in situ hybridization and ribonuclease protection assay methods, we studied NT-3 mRNA expression in rats with and without DEX administration after transient forebrain ischemia. Without DEX treatment, NT-3 mRNA was down-regulated in the hippocampal neurons at 2, 4, 12 h and returned to basal levels 24 h following ischemia. With DEX treatment, however, NT-3 mRNA showed no change at 2, 4 and 12 h and increased 24 h after ischemia. The results indicate that DEX inhibits ischemia-induced NT-3 mRNA down-regulation during the first 12 h and up-regulates NT-3 mRNA 24 h after ischemia. DEX administration might be effective in influencing some of the pathophysiological effects of ischemia in the hippocampus.
SO Neuroreport, (**Oct. 26, 1998**) Vol. 9, No. 15, pp. 3477-3480.
ISSN: 0959-4965.

L11 ANSWER 10 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
5
TI Regulation of glial cell line-derived neurotrophic factor release from rat
C6 glioblastoma cells.
AB We have monitored glial cell line-derived neurotrophic factor (GDNF) secretion from rat C6 glioblastoma cells by ELISA. Representative cytokines, **neurotrophins**, growth factors, neuropeptides, and pharmacological agents were tested for their ability to modulate GDNF release. Whereas most factors tested had minimal effect, a 24-h treatment with fibroblast growth factor-1, -2, or -9 elevated secreted GDNF protein levels five- to 10-fold. The proinflammatory cytokines interleukin-1beta, interleukin-6, tumor necrosis factor-alpha, and lipopolysaccharide elevated GDNF release 1.5- to twofold. Parallel studies aimed at elucidating intracellular events that may regulate GDNF synthesis/release demonstrated the involvement of multiple signaling pathways. GDNF levels were increased by phorbol 12,13-didecanoate (10 nM) activation of protein kinase C, the Ca2+ ionophore A23187 (1 muM), okadaic acid (10 nM) inhibition of type2A protein phosphatases, nitric oxide donors (1 mM), and
H2O2 (1 mM)-induced oxidative stress. Elevation of cyclic AMP levels by either forskolin (10 muM) or dibutyryl cyclic AMP (1 mM) repressed GDNF secretion, as did treatment with the glucocorticoid **dexamethasone** (1 muM). Our results demonstrate that diverse biological factors are capable of modulating GDNF protein levels and that multiple signal transduction systems can regulate GDNF synthesis and/or release.
SO Journal of Neurochemistry, (**Feb., 1998**) Vol. 70, No. 2, pp. 531-539.
ISSN: 0022-3042.

L11 ANSWER 11 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI **Dexamethasone** decreases P75NTR expression in injured spinal cord.
SO Society for Neuroscience Abstracts, (1998) Vol. 24, No. 1-2, pp. 290.
Meeting Info.: 28th Annual Meeting of the Society for Neuroscience, Part 1
Los Angeles, California, USA November 7-12, 1998 Society for Neuroscience. ISSN: 0190-5295.

L11 ANSWER 12 OF 26 CAPLUS COPYRIGHT 2003 ACS
TI Pharmacology of apoptosis in the central nervous system
AB A review with 43 refs., focusing on the mol. mechanisms of apoptosis in the cental nervous system and the recent development concerning three hypotheses about them: killer-genes' expression, abortive cell cycle and alterations in mitochondria. Cell death plays an important role in both normal and pathol. phenomena. It has been classified into two types: accidental (necrosis) and programmed (apoptosis). Programmed cell death is a physiol. process, typically marked by nuclear condensation and DNA fragmentation. The role of **neurotrophins**, P53 and Bcl2-family of proteins, tyrosine kinases, cytokines, etc is discussed. It has been shown that various drugs can affect the apoptotic death cascade and can prevent or stimulate apoptosis. The effects of **neurotrophins**, **dexamethasone**, glutamate, cytosine- arabinoside, 5-azacytidine, cisplatin, etc. on the different pathways of the apoptosis in the cental nervous system is discussed.
SO Farmatsiya (Sofia) (**1998**), 45(2), 31-38
CODEN: FMTYA2; ISSN: 0428-0296

L11 ANSWER 13 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Effect of glucocorticoid on NGF-stimulated TrkA signaling in PC12 cells.
SO Society for Neuroscience Abstracts, (1997) Vol. 23, No. 1-2, pp. 1702.
Meeting Info.: 27th Annual Meeting of the Society for Neuroscience New Orleans, Louisiana, USA October 25-30, 1997
ISSN: 0190-5295.

L11 ANSWER 14 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 6
TI Expression of nerve growth factor and **neurotrophin** receptors in testicular cells suggest novel roles for **neurotrophins** outside the nervous system.
AB The present study was designed to clarify the non-neurotrophic role for **neurotrophins** in mouse testis. By means of S1 nuclease protection assay we could demonstrate that the gene coding for the low-affinity nerve growth factor (NGF) receptor p75-NGFR is transiently expressed during germ cell development. Gene expression for p75-NGFR was detected in late-meiotic spermatocytes and early spermatids and was found to be co-expressed with trkB and trkC, two tyrosine kinase receptors, commonly regarded as the high-affinity receptors for brain-derived neurotrophic factor and **neurotrophin**-3. Gene transcripts for the high-affinity NGF receptor trkA were found exclusively in non-germ cells. Isolated Leydig cells, peritubular myoid cells and Sertoli cells, but not germ cells, could be identified as potential testicular NGF sources. Non-germ cells respond after incubation for several days with a sharp induction in NGF synthesis, which is accompanied by a loss of phenotypic expression patterns. The fact that p75-NGFR mRNA expression was induced in cultured Sertoli cells and peritubular myoid cells suggests an autocrine mode of NGF action in these cells. Induction of NGF synthesis in cultured Leydig cells could be prevented by the glucocorticoid **dexamethasone**. Results indicate different roles for the individual **neurotrophins** in distinct testicular compartments and suggest that these **neurotrophins** might support testicular functions by signalling between individual cell types in an autocrine and paracrine manner.
SO Reproduction Fertility and Development, (1996) Vol. 8, No. 7, pp. 1075-1087.
ISSN: 1031-3613.

L11 ANSWER 15 OF 26 CAPLUS COPYRIGHT 2003 ACS
TI Modulation of **neurotrophins** and their receptors by adrenal steroids
AB A review, with 114 refs., on: the nerve growth factor family and their receptors; effects of glucocorticoids on **neurotrophin** expression in culture; effects of **dexamethasone** administration on **neurotrophin** expression in vivo; adrenalectomy and **neurotrophins**; and **neurotrophin** receptors and adrenal steroids.
SO CNS Neurotransmitters and Neuromodulators: Neuroactive Steroids (**1996**), 113-125. Editor(s): Stone, Trevor W. Publisher: CRC Press, Boca Raton, Fla.
CODEN: 62YCAC

L11 ANSWER 16 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 7
TI **Neurotrophin** expression modulated by glucocorticoids and oestrogen in immortalized hippocampal neurons.
AB We have used reverse transcription followed by polymerase chain reaction amplification to investigate changes in expression of nerve growth factor (NGF) mRNA in immortalized hippocampal neurons after treatment with the glucocorticoids **dexamethasone** and corticosterone, the glucocorticoid antagonist RU38486, and the gonadal steroids progesterone and 17-beta oestradiol. We found that NGF mRNA levels rise after application of either **dexamethasone** or corticosterone, and that this rise is prevented by the antagonist. Thus, **neurotrophin** expression is modulated by the physiological glucocorticoid and is mediated by type II glucocorticoid receptors. Progesterone has no effect, while 17-beta oestradiol suppresses NGF mRNA in a postnatally-derived cell line but does not change levels in an embryonic line. An increase in **neurotrophin** expression is therefore not a general response to steroid hormone application, and may be a specific defence against the presence of metabolically endangering glucocorticoids.
SO Molecular Brain Research, (1995) Vol. 31, No. 1-2, pp. 158-164.
ISSN: 0169-328X.

L11 ANSWER 17 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI **Neurotrophin**-R inhibits lipopolysaccharide-induced nitric oxide production in cultured human endothelial cells.
SO Cell Structure and Function, (1994) Vol. 19, No. 6, pp. 555.
Meeting Info.: Forty-seventh Annual Meeting of the Japan Society for Cell Biology Nagasaki, Japan September 28-30, 1994
ISSN: 0386-7196.

L11 ANSWER 18 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 8
TI **Neurotrophins** and their receptors in the rat pituitary gland: Regulation of BDNF and trkB mRNA levels by adrenal hormones.
AB We studied the expression of messenger ribonucleic acids (mRNAs) for **neurotrophins** and **neurotrophin** receptors in the rat pituitary gland and examined the influence of adrenal hormones on their mRNA levels, using in situ hybridization and Northern blot analysis. The only **neurotrophin** present at detectable levels in the pituitary was brain-derived neurotrophic factor (BDNF), which was observed in the anterior and intermediate lobes. Several transcripts of the putative receptor for BDNF, trkB, were present in the anterior and posterior lobes of the pituitary. A low amount of irk C mRNA was found in both the

anterior and the intermediate lobe. **Dexamethasone** treatment decreased both BDNF and trkB mRNA levels in the anterior lobe of the pituitary. Adrenalectomy had no effect on trk B expression, but it decreased BDNF mRNA levels in comparison to the control animals. This effect could not be reversed by **dexamethasone** substitution, suggesting that BDNF mRNA levels may be regulated not only by glucocorticoids but also by other adrenal hormones. These results demonstrate that BDNF, trkB and trkC are expressed in the pituitary gland and that glucocorticoids and possibly other adrenal hormones may modulate pituitary functions by regulating the expression of neurotrophic factors and their receptors. Whether BDNF acts as a secreted hormone, a trophic factor, or has autocrine/paracrine functions within the pituitary through its receptor, trkB, remains to be studied.

SO Molecular Brain Research, (1994) Vol. 27, No. 2, pp. 347-354.
ISSN: 0169-328X.

L11 ANSWER 19 OF 26 MEDLINE

TI Glucocorticoids and **neurotrophin** gene regulation in the nervous system.

SO ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, **(1994 Nov 30)** 746 195-202; discussion 202-3. Ref: 34
Journal code: 7506858. ISSN: 0077-8923.

L11 ANSWER 20 OF 26 CAPLUS COPYRIGHT 2003 ACS

TI Therapy of central nervous system by genetically modified cells

AB A method for treating defective, diseased, or damaged cells in the mammalian central nervous system (CNS) comprises grafting donor cells into the CNS. The donor cells are genetically modified (e.g. by insertion of .gtoreq.1 therapeutic gene) to produce functional mols. in a sufficient amt. to ameliorate the defective, diseased, or damaged cells in the CNS. Methods and vectors for carrying out gene transfer and grafting are described. The retroviral vector pLThRNL, a Moloney leukemia virus-derived retroviral vector, was constructed expressing the rat cDNA for tyrosine hydroxylase (TH) from the 5' LTR sequence and contg. a neomycin-resistance gene transcribed from an internal RSV promoter. The retroviral vector was transfected into producer cells to produce virus LThRNL carrying the gene encoding TH. Immortalized rat fibroblasts were infected with LThRNL and cells were selected for expression of the neomycin-resistance gene by growth in 400 .mu.g/mL of G-418. Fibroblasts expressing TH produced L-DOPA when cultured in media supplemented with 6-methyl-5,6,7,8-tetrahydropterin. When the DOPA-producing fibroblasts were implanted into the rostral caudate region, they reduced the rotational asymmetry in the rat model of Parkinson's disease.

SO PCT Int. Appl., 225 pp.
CODEN: PIXXD2

L11 ANSWER 21 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI Different forms of the **neurotrophin** receptor trkB mRNA predominate in rat retina and optic nerve.

AB The expression of TrkB mRNAs was investigated in rat retina and optic nerve. A 11.5 kb transcript that encodes full-length TRKB was found to predominate in Northern blots of retinal RNA. By in situ hybridization, this trkB expression wag concentrated in the ganglion cell and inner nuclear layers. Furthermore, an antibody to the full-length TRKB immunostained retinal ganglion cells and their axons. In contrast, Northern blots of optic nerve RNA showed a prominent 9.5 kb band that encoded a form of the TRKB receptor lacking the tyrosine kinase domain. This species was also detected in both the sciatic nerve and cultured astrocytes and C6 glioma cells. These results suggest that neurons express

the full-length TRKB containing the tyrosine kinase domain, while nonneuronal cells express the truncated form of the receptor. These two classes of TRKB may mediate different neurotrophic actions in the retina and optic nerve.

SO Journal of Neurobiology, (1993) Vol. 24, No. 9, pp. 1207-1214.
ISSN: 0022-3034.

L11 ANSWER 22 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 9

TI Adrenalectomy attenuates kainic acid-elicited increases of messenger RNAs for **neurotrophins** and their receptors in the rat brain.

AB Treatment with excitotoxin kainic acid is known to increase the level of messenger RNAs for nerve growth factor and brain-derived neurotrophic factor in the brain. In this study we have used quantitative in situ hybridization to analyse the effect of glucocorticoids on kainic acid-induced increase of nerve growth factor and brain-derived neurotrophic factor messenger RNA in the rat brain. In adrenalectomized animals, the kainic acid-mediated increase of brain-derived neurotrophic factor messenger RNA in the hippocampus and the cerebral cortex was reduced by 50% compared to sham-operated animals. The increase of nerve growth factor messenger RNA elicited by kainic acid in the dentate gyrus was almost completely abolished in adrenalectomized animals. No significant change was seen in c-fos messenger RNA in the hippocampus of adrenalectomized rat after kainic acid injection compared to sham-operated kainic acid-treated rats, while a three-fold reduction was seen in the cerebral cortex. **Dexamethasone** injection prior to kainic acid administration potentiated the kainic acid-induced increase of nerve growth factor messenger RNA in the dentate gyrus and the piriform cortex. In contrast, **dexamethasone** pretreatment did not potentiate the kainic acid-mediated increase of brain-derived neurotrophic factor messenger RNA. We also examined the effect of adrenalectomy and kainic acid injection on tropomyosin receptor kinase B and C messenger RNA, encoding essential components of high-affinity receptor for brain-derived neurotrophic factor/**neurotrophin**-4 and **neurotrophin**-3, respectively. Following adrenalectomy no change of tropomyosin receptor kinase B or C messenger RNA was detected in any of the brain regions studied compared to sham-operated animals. The injection of kainic acid caused four-fold and two-fold increases of tropomyosin receptor kinase B messenger RNA in the dentate gyrus and cerebral cortex, respectively, but no change in tropomyosin receptor kinase C messenger RNA in any of these regions. In adrenalectomized animals receiving kainic acid, the level of tropomyosin receptor kinase B messenger RNA was decreased both in the dentate gyrus and cerebral cortex as compared to sham animals treated with kainic acid. Taken together, the data suggest that excitotoxins and glucocorticoids both influence expression of brain-derived neurotrophic factor and nerve growth factor messenger RNA in the brain, but by two different mechanisms, where the effect of excitotoxin-evoked seizures is modulated by glucocorticoids.

SO Neuroscience, (1993) Vol. 54, No. 4, pp. 909-921.
ISSN: 0306-4522.

L11 ANSWER 23 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 10

TI Glucocorticoids depress activity-dependent expression of BDNF mRNA in hippocampal neurones.

AB Glucocorticoid hormones are important regulators of brain development and ageing, and can impair the capacity of hippocampal neurones to survive

various neurological insults. Here we show that **dexamethasone**, a synthetic glucocorticoid, prevents activity-dependent increases of brain-derived neurotrophic factor (BDNF) mRNA in cultures of rat hippocampal neurones. In situ hybridization was used to evaluate the levels of BDNF mRNA. Up-regulation of BDNF mRNA triggered by depolarization with high potassium, or exposure to the glutamate receptor agonist kainic acid, resulted both from higher levels of expression in neurones and from new recruitment of cells. These data suggest that the known ability of glucocorticoids to exacerbate neuronal injury following ischaemia and other metabolic insults could be due to antagonism of regulatory mechanisms governing **neurotrophin** levels in the brain.

SO Neuroreport, (1993) Vol. 4, No. 5, pp. 527-530.
ISSN: 0959-4965.

L11 ANSWER 24 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI Modulation of **neurotrophin** expression by glucocorticoids in immortalized hippocampal neurons.

SO Society for Neuroscience Abstracts, (1993) Vol. 19, No. 1-3, pp. 256.
Meeting Info.: 23rd Annual Meeting of the Society for Neuroscience Washington, D.C., USA November 7-12, 1993
ISSN: 0190-5295.

L11 ANSWER 25 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 11

TI Glucocorticoid modulation of **neurotrophin** expression in immortalized mouse hippocampal neurons.

AB To see whether glucocorticoid hormones can influence the regulation of **neurotrophin** expression in hippocampal neurons, we have used reverse-transcription followed by polymerase chain reaction to investigate changes in the mRNA levels of nerve growth factor (NGF) and **neurotrophin**-3 (NT-3) in immortalized hippocampal neurons after **dexamethasone** application. Our results show that NGF mRNA levels rise in both embryonic and postnatal neurons, but with different time courses, while NT-3 levels rise in the embryonic but not in the postnatally derived cell line. Modulation of NT expression by glucocorticoids may therefore be developmentally regulated.

SO Neuroscience Letters, (1993) Vol. 155, No. 1, pp. 11-14.
ISSN: 0304-3940.

L11 ANSWER 26 OF 26 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI REGULATION OF **NEUROTROPHIN** MRNA EXPRESSION IN THE RAT BRAIN BY GLUCOCORTICOIDS.

AB Northern blot analysis was used to examine the effects of glucocorticoids on **neurotrophin** mRNA expression in the rat cerebral cortex and hippocampus. The results show that 3 days after adrenalectomy the mRNA levels for nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and **neurotrophin**-3 (NT-3) decreased significantly in both these regions. In adrenalectomized animals given **dexamethasone** replacement the mRNA levels for the three **neurotrophins** were restored to control levels. The effect of a single dose of **dexamethasone** (5 mg/k) administered i.p. to intact animals on the expression of **neurotrophins** was also examined. NGF and NT-3 mRNAs showed a 2.5-fold and a 1.4-fold increase, respectively, during the first 4 h after the injection. The increase was followed by a decrease, with levels .apprx. 50% of control 24 and 48 h after the injection. In contrast, the level of BDNF mRNA did not change during the first 10 h after the injection, but decreased to 70% of control 48 h after the injection. These data indicate that glucocorticoids regulate

neurotrophin mRNA expression both in the cortex and in the hippocampus, and suggest further that the known effects of glucocorticoids on neuronal survival in the brain could be due to changes in the levels of neurotropins in the brain.

SO EUR J NEUROSCI, (1992) 4 (5), 396-403.
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